REMARKS

Claims 14, 15, 19 and 21-36 are pending. Favorable reconsideration is respectfully requested.

The rejection of Claims 21, 24 and 26-36 under 35 U.S.C. §112, first paragraph, for an alleged lack possession as set forth at pages 2 and 3 of the Official Action dated June 25, 2003, is respectfully traversed.

The phrase "deletion of amino acids 297-329 in said variable loop" recited in Claims 21, 24, 26, 27, 30, and 34 is not new matter.

Applicants submit herewith the executed Rule 132 Declaration of Dr. Alagarsamy Srinivasan. Dr. Srinivasan has years of experience in the field of AIDS pathogenesis and vaccines. See paragraph (1) of the Declaration.

Dr. Srinivasan has read and understood the contents of the present application. In addition, he appreciates that the present application was filed on May 29, 1998. Dr. Srinivasan has also read and understood the pending claims of the present application as well as the Official Action dated June 25, 2003. See paragraphs (4)-(21) of the Declaration.

According to Dr. Srinivasan, the amino acid sequence of the envelope glycoprotein of HIV was well-known to those skilled in the field of the invention at the time the present application was filed in the U.S. In particular, the location of the hypervariable region of the amino acid sequence was well-known to those skilled in the field of the invention. In addition, it was well-known to those skilled in the field of the invention that the third variable loop (V3) of includes amino acids 297 to 329. Therefore, in Dr. Srinivasan's opinion, those skilled in the field of the invention at the time the present application was filed in the U.S would have appreciated that those numbers refer to the amino acid sequence of the protein, and do not refer to the nucleic acid sequence encoding that protein. According to Dr. Srinivasan, this is demonstrated by Back et al., *Journal of Virology*, Nov. 1993, pp. 6897-

6902, a copy of which is attached to the Declaration as Exhibit 2. According to Dr. Srinivasan, Back et al. describe the gp41 coding region and the hypervariable region. See Figure 2 at page 6900 of Back et al., which explicitly describes that amino acids 297 to 329 are part of V3, i.e., the third variable loop. See paragraph (21) of the Declaration.

In Dr. Srinivasan's opinion, those skilled in the field of the invention at the time the present application was filed in the U.S would have appreciated that the vv-ΔV3 mutant with the Δ297-329 deletion prepared in Example 2 of the present application was a construct in which amino acids 297-329 of V3 were replaced with Gly-Ala-Gly. According to Dr. Srinivasan, this is demonstrated by the fact that Example 2 of the present application describes that the vv-ΔV3 mutant was constructed from ligation of fragments obtained by PCR amplification from the pSVIII-env plasmid, which was a gift from Dr. J. Sodroski (see page 26 of the present application). According to Dr. Srinivasan, the pSVIII-env plasmid is described in a scientific publication co-authored by Dr. Sodroski: Wyatt et al., Journal of Virology, Dec. 1992, pp. 6997-7004, a copy of which is attached to the Declaration as Exhibit 3. The first paragraph of the Materials and Methods section of Wyatt et al. reads as follows:

> Mutant envelope glycoproteins. The HIV-1 (HXBc2 strain) envelope glycoprotein mutants used in this study were previously described (46). The Δ297-329 mutant contains a deletion spanning the V3 loop, with the sequence Gly-Ala-Gly inserted in place of the loop (62, 68). Envelope glycoproteins were expressed by transfection of ***plasmid pSVIII-env*** containing either a wild-type or mutated env gene into COS-1 cells by the DEAE-dextran technique (46). [Emphasis added.]

Thus, according to Dr. Srinivasan, Wyatt et al. explicitly states that the Δ297-329 mutant described in Example 2 of the present application had amino acid residues 297-329 replaced with Gly-Ala-Gly. Wyatt et al. also makes it apparent that the numbers "297-329" refer to

amino acids in the protein sequence and not to base positions in the encoding nucleic acid sequence. See paragraph (22) of the Declaration.

Based on the foregoing, the phrase "deletion of amino acids 297-329 in said variable loop" recited in Claims 21, 24, 26, 27, 30, and 34 is not new matter.

Regarding the phrase "introducing into a vector DNA or liposome a nucleic acid encoding an envelope...," it is Dr. Srinivasan's opinion that the specification of the present application provides support for that phrase at page 4, lines 14-15. See paragraph (24) of the Declaration. Indeed, that portion of the specification provides explicit support for that phrase.

Regarding APCs with adjuvant, it is Dr. Srinivasan's opinion that the specification of the present application provides support for that phrase at page 4, lines 20-23. See paragraph (25) of the Declaration. Indeed, that portion of the specification provides explicit support for that phrase.

Based on the foregoing, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 14, 15, 19 and 21-36 under U.S.C. §112, first paragraph, for an alleged lack of possession as set forth at pages 4-9 of the Official Action dated June 25, 2003, is respectfully traversed.

According to Dr. Srinivasan, the generation of the 1ΔV3, 7ΔV3, and 8ΔV3 mutants has been described by Kmieciak et al., J. Immunol. 1998, 160:5676-5683 in the Materials and Methods section (a copy of Kmieciak et al. is attached to the Declaration as Exhibit 6). Dr. Srinivasan summarizes that method as follows. See paragraph (23) of the Declaration.

The HIV-1IIIB isolate was the source of the wild-type (WT) envelope (env) gene and the ΔV3 env mutant cloned in the pSC11-based vector under the control of a synthetic early/late vaccinia virus (vv) promoter. The 1ΔV3, 7ΔV3, and 8ΔV3 mutants are

recombinant vv clones generated by homologous recombination of the pSC-ΔV3 plasmid using nonrecombinant vaccinia virus. They all express the Δ297-329 deletion of the env glycoprotein. See paragraph (23) of the Declaration.

The pSC-ΔV3 env plasmid was constructed by ligation of fragments obtained by PCR amplification from the pSVIII-env plasmid. One fragment was generated by PCR with the synthetic oligonucleotide containing the *Sal*I site and the CCACC Kozak's sequence in front of the ATG condon (5'-AGAGTCGACCCACCATGAGAGTGAAGGAGA-3', sense) and with the oligonucleotide (5'-ACAGGTACCCCATAATAGACTGTGAC-3', antisense) containing the *Kpn*I site. The second fragment was derived by *Kpn*I and *BamH*I digests of the pSVIII-env plasmid, and the third fragment was generated by PCR with the synthetic oligonucleotide containing the *BamH*I site at its 5' end (5'-AACGGATCCTTAGCACTTATCTGGG-3', sense) and the antisense primer (5'-TTGCGCGGCCGCTTATAGCAAAATCCTTTCC-3') containing the TAA stop codon followed by the *Not*I site. The three fragments were ligated into the *Sal*I and *Not*I sites of the pSC-11-based vector to generate plasmid pSC-ΔV3. A similar approach was used to generate plasmid with the WT env gene (pSC-WTP) using the recombinant clone pIIIB. Plasmids pSC-ΔV3 and pSC-WTP were used to generate recombinant vv-ΔV3 (1ΔV3, 7ΔV3, 8ΔV3) and vv-WTP (WTP-2, WTP-5, and WTP-8) viruses by homologous recombination. Note, that only vv-WTP-2 and vv-7ΔV3 were used for functional studies including env-specific cytotoxic T cell responses and HIV gp120-mediated pathogenesis. See paragraph (23) of the Declaration.

As discussed above, it is Dr. Srinivasan's opinion that those skilled in the field of the invention at the time the present application was filed in the U.S would have appreciated that the vv-ΔV3 mutant with the Δ297-329 deletion prepared in Example 2 of the present

application was a construct in which amino acids 297-329 of V3 were replaced with Gly-Ala-Gly.

In Dr. Srinivasan's opinion, the specification of the present application provides a detailed description of procedures for making the nucleic acid and cells recited in the Claims 14, 15, 19, and 21-36 of the present application and a description of how to use those cells for preparing a vaccine against HIV, for inducing cellular immunity against HIV, stimulating CTL activity against HIV, and stimulating a CTL response in a patient as specified in those claims. According to Dr. Srinivasan, one skilled in the field of the invention would have appreciated at the time the present application was filed in the U.S. that the inventors thereof were in possession of the invention as defined in the claims of the present application and that those inventions could be practiced using routine experimentation. See paragraph (26) of the Declaration. Therefore, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 14, 15, 19 and 21-36 under U.S.C. §112, first paragraph, for an alleged lack of enablement as set forth at pages 9-15 of the Official Action dated June 25, 2003, is respectfully traversed.

Based on his review of the present application (see paragraphs (5)-(18) of the Declaration), it is Dr. Srinivasan's opinion that the specification of the present application provides a detailed description of procedures for making the nucleic acid and cells recited in the Claims 14, 15, 19, and 21-36 of the present application and a description of how to use those cells for preparing a vaccine against HIV, for inducing cellular immunity against HIV, stimulating CTL activity against HIV, and stimulating a CTL response in a patient as specified in those claims. See paragraph (26) of the Declaration.

In addition, according to Dr. Srinivasan, several articles were published after the present application was filed in the U.S. and demonstrate that the methods and procedures

described in the present application described how to make and use compositions as specified in Claims 14, 15, 19, and 21-36 of the present application. Those publications are:

(a) Rowland-Jones et al., *Immunology Letters*, 1999, 00. 9-14 (a copy of which is attached to the Declaration as Exhibit 4);

(b) Kiszka et al., *Journal of Virology*, May 2002, pp. 4222-4232 (a copy of which is attached to the Declaration as Exhibit 5); and

(c) Kmieciak et al., *The Journal of Immunology*, 1998, pp. 5676-5683 (a copy of which is attached to the Declaration as Exhibit 6).

According to Dr. Srinivasan, Rowland-Jones et al. states that eliciting a CTL response is an important goal for developing a vaccine against HIV. See the Abstract and paragraph (28) of the Declaration.

Kiszka et al. is co-authored by the two inventors of the present application, i.e., Yutaro Kaneko and Danuta Kozbor. Kiszka et al. demonstrate the "vaccines expressing the ΔV3 mutant of either HIV -1IIIb or HIV-189.6 envelope glycoproteins induced broader CD8+ T-cell activities than those elicited by the wildtype (WT) counterparts." See the Abstract and paragraph (29) of the Declaration.

Kmieciak et al. is also co-authored by the two inventors of the present application. Kmieciak et al. describe that the ΔV3 mutant described in the present application increased CTL activities against conserved epitopes of the env glycoprotein. See the Abstract and paragraph (30) of the Declaration.

In view of the foregoing, the claims are enabled. Withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 21, 24 and 26-36 under 35 U.S.C. §112, second paragraph as set forth at page 16 of the Official Action, is respectfully traversed.

As discussed above, it is Dr. Srinivasan's opinion that those skilled in the field of the invention at the time the present application was filed in the U.S would have appreciated that the vv-ΔV3 mutant with the Δ297-329 deletion prepared in Example 2 of the present application was a construct in which amino acids 297-329 of V3 were replaced with Gly-Ala-Gly.

According to Dr. Srinivasan, the phrase "introducing into a vector DNA or liposome a nucleic acid encoding an envelope glycoprotein of HIV," as recited in Claim 28, would not have been unclear to those skilled in the art when the present application was filed in the U.S. That phrase simply means that a nucleic acid which encodes an envelope glycoprotein of HIV is introduced into a vector DNA or liposome. See paragraph (31) of the Declaration.

In Dr. Srinivasan's opinion, the meaning of the term "introducing" such a nucleic acid into a vector DNA or liposome, as recited in Claim 28, was well-known in the field of the invention at the time the present application was filed in the U.S. Moreover, the specification of the present application explains such a procedure in detail, and even provides specific Examples thereof. See paragraph (32) of the Declaration.

According to Dr. Srinivasan, the fact that Claim 28 recites vector DNA or liposome as alternatives would not have confused those skilled in the art when the present application was filed in the U.S., because there is nothing confusing about the meaning of two alternatives in the claim. See paragraph (33) of the Declaration.

In Dr. Srinivasan's opinion, the meaning of the term "vector DNA" as recited in Claim 28 would have been readily appreciated by those skilled in the field of the invention at the time the present application was filed in the U.S. That term is defined in the specification of the present application at page 9, lines 20-21. See paragraph (34) of the Declaration.

According to Dr. Srinivasan, the meaning of Claim 29 would have been readily appreciated by those skilled in the field of the invention at the time the present application

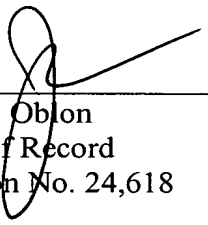
was filed in the U.S. It would have been appreciated that the adjuvant recited in Claim 29 could be the same as or different from the adjuvant specified in Claim 28. See paragraph (35) of the Declaration.

Based on the foregoing, the claims are definite within the meaning of 35 U.S.C. §112, second paragraph. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is now in condition for allowance and early notice of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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